INPLASY PROTOCOL

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Conflicts of interest:
None declared.

A meta-analysis of association between CCL5、CCL11、CCL17 polymorphisms and AD

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Review question / Objective: **At present, many studies on the association between CCL5、CCL11、CCL17 polymorphisms and atopic dermatitis（AD）are inconsistent. We conducted this meta-analysis of Case control trial to evaluate the association between CCL5、CCL11、CCL17 polymorphisms and atopic dermatitis（AD).**

Condition being studied: **Since the discovery of cytokines, and in particular the role of chemokines in the progression of AD, many clinical studies have been carried out around the world to explore the association of AD with chemokine polymorphism. However, the quality, type and conclusions of studies on the correlation between chemokine polymorphism and AD are inconsistent. Foreign studies have shown that chemokine polymorphism is statistically significant in relation to AD. Studies by Menzies-Gow A et al have shown that a new therapeutic strategy targeting to block CCL11 signal has been proven to significantly improve patients with moderate to severe AD. However, some foreign studies have also reported that chemokine polymorphism is unrelated to AD.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 November 2022 and was last updated on 29 November 2022 (registration number INPLASY2022110148).

INTRODUCTION

Review question / Objective: **At present, many studies on the association between CCL5、CCL11、CCL17 polymorphisms and atopic dermatitis（AD）are inconsistent. We conducted this meta-analysis of Case control trial to evaluate the association between CCL5、CCL11、CCL17 polymorphisms and atopic dermatitis（AD).**

Rationale: **Atopic dermatitis is a common chronic and recurrent skin inflammatory disease with high heterogeneity and**

heredity. It is characterized by dryness, recurrence, pruritus and eczematous skin lesions, and it has caused a huge burden on medical resources. Although the exact cause of AD is still unclear, genetic susceptibility such as interleukin type, chemokines and environmental factors such as microorganisms (Malassezia), plays an important role in the occurrence and development of AD. AD is mediated by type 2 T helper cells (Th2). Specific immune and inflammatory mechanisms play an important role in the development of AD, and the abnormal production of cytokines and chemokines is related to its pathogenesis.Chemokine genes are a group of cytokines that help cells migrate, grow, differentiate, and regulate the inflammatory and anti-inflammatory responses of the immune system .The chemokines are the most potent molecules regulating the selective recruitment of leukocytes into inflamed lesions. In addition, some chemokines also affect interleukin (IL) production, angiogenesis, and collagen production. Based on a cysteine motif, CXC, CC, C, and CX3C families have been identified. CC (or β) chemokines exert their action on multiple leukocyte subsets, including monocytes, basophils, T cells, dendritic cells, and natural killer cells.

Condition being studied: Since the discovery of cytokines, and in particular the role of chemokines in the progression of AD, many clinical studies have been carried out around the world to explore the association of AD with chemokine polymorphism. However, the quality, type and conclusions of studies on the correlation between chemokine polymorphism and AD are inconsistent. Foreign studies have shown that chemokine polymorphism is statistically significant in relation to AD. Studies by Menzies-Gow A et al have shown that a new therapeutic strategy targeting to block CCL11 signal has been proven to significantly improve patients with moderate to severe AD. However, some foreign studies have also reported that chemokine polymorphism is unrelated to AD.

METHODS

Search strategy: Embase, Pubmed, Cochrane Library, CBM, CNKI, VIP and Wanfang databases were searched, and all Chinese or English publications on Association between CCL5、CCL11、CCL17 polymorphisms and AD before October 27, 2022 were retrieved. Chinese and English search terms are combined with free words and combined according to Boolean logic (see the appendix for details).

Participant or population: The research objective was any patient who was diagnosed with AD by a doctor in accordance with the Hanifin and Rajka (1980) diagnostic criteria and the British revised Williams (1994) diagnostic criteria. Age and gender were not limited. And healthy control group matching the case group.

Intervention: None.

Comparator: None.

Study designs to be included: Case-control studies of the correlation between chemokine polymorphism and AD was included. They were divided into case group and control group according to whether they had AD or not.The measure is to detect the genes and genotypes of chemokines in the study subjects. The main outcome was chemokine gene frequency.The research objective was any patient who was diagnosed with AD by a doctor in accordance with the Hanifin and Rajka (1980) diagnostic criteria and the British revised Williams (1994) diagnostic criteria. And healthy control group matching the case group.Age and gender were not limit.

Eligibility criteria: The research objective was any patient who was diagnosed with AD by a doctor in accordance with the Hanifin and Rajka (1980) diagnostic criteria and the British revised Williams (1994) diagnostic criteria. Age and gender were

not limited. And healthy control group matching the case group.

Information sources: Embase, Pubmed, Cochrane Library, CBM, CNKI, VIP and Wanfang databases were searched, and all Chinese or English publications on Association between CCL5、CCL11、CCL17 polymorphisms and AD before October 27, 2022 were retrieved. Two researchers independently extracted the data on the basis of the data extraction table that was drawn up in advance. The basic content that was extracted was as follows: (1) first author, year of publication, country, and region; (2) characteristics of the research objectives; (3) outcome indicators and research results.

Main outcome(s): Because the case control studies were included in this meta-analysis were not verified in multiple studies and most of the studies were poor quality and had incomplete data, it is currently not possible to accurately evaluate the association between CCL5、CCL11、CCL17 polymorphisms and AD. It requires more high-quality large-sample case control studies to confirm the results. In future clinical research. The severity and location of the study patients should be fully described to analyze different subgroups.A total of 7 articles were finally screened out, including 1316 AD patients and 1099 controls. The research objective was any patient who was diagnosed with AD by a doctor in accordance with the Hanifin and Rajka (1980) diagnostic criteria and the British revised Williams (1994) diagnostic criteria. Age and gender were not limited.And healthy control group matching the case group. Based on whether had AD or not, patients were divided into two subgroups (AD group and healthy control group) .The bias risk results showed that some studies had incomplete data and selectively reported research results. Quantitative analysis results showed that a significant association between the CCL5 –403G/A polymorphism and AD under the heterozygous model (AG vs. GG: OR=1.40, 95% CI=1.08-1.80, P=0.01) and dominant model (AA+AG vs. GG: OR=1.38, 95% CI=1.08-1.76, P=0.01) in a fixed-effect model. The dominant model (GG+GC vs.CC: OR=1.74, 95% CI=1.23-2.47, P=0.002) and allele model (G vs. C: OR=1.46, 95% CI=1.07-1.98, P=0.02) of CCL5 –28C/Gpolymorphism was also associated with increased the risk of AD. However, this significant association was not found in other genotypes (P>0.05).

Additional outcome(s): None.

Data management: NoteExpress document manager was used to screen out the duplicate studies. The risk of bias was assessed using the “risk of bias assessment” tool that is recommended by the Cochrane Collaboration. Review Manager 5.4 was used to analyze the data.

Quality assessment / Risk of bias analysis: The risk of bias was assessed using the “risk of bias assessment” tool that is recommended by the Cochrane Collaboration. Any disagreements between the two researchers were discussed and resolved between the two researchers or handed over to a third party for a ruling.

Strategy of data synthesis: Binary variables are presented as the relative risk (RR) and the 95% confidence interval (CI), while numerical variables are presented as the mean difference (MD) and the 95%CI. Research data with the same intervention type were merged, and the heterogeneity was evaluated before merging the data. If the heterogeneity test results showed P > 0.1 and I2 ≤ 50%, the fixed-effects model was used to calculate the merged statistics. However, if the heterogeneity test showed P ≤ 0.1 and I2 > 50%, the random-effects model was used. The Z test or the CI method was used to test whether the combined results were statistically significant. If P ≤ 0.05 using the Z test, the upper and lower limits of the 95%CI for the RR do not include one or the upper and lower limits of the 95%CI of the MD. If zero is not included, the combined result is statistically significant. However, if P > 0.05 using the Z test, the 95%CI of the RR contains one, or the 95%CI of the MD contains zero, then the combined result is

not statistically significant. When the number of studies for which the data could be merged was not less than ten, a funnel chart was used to analyze the publication bias. If the data could not be merged, they were described qualitatively.

Subgroup analysis: A case-control study of the correlation between chemokine polymorphism and AD was included. They were divided into case group and control group according to whether they had AD or not. The main outcome was chemokine gene frequency.(The gene frequency of the case group was higher than that of the control group, and the $p < 0.05$.)

Sensitivity analysis: None.

Language restriction: The study was in Chinese or English.

Country(ies) involved: China (Chengdu Medical College and The First Affiliated Hospital of Chengdu Medical College).

Keywords: atopic dermatitis, chemokines, polymorphism, meta-analysis.

Contributions of each author:

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